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Uremic toxins and peritoneal dialysis

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Uremic toxins and peritoneal dialysis. Uremic toxicity is related in part to the accumulation of toxic substances, the nature of which has only partly been characterized. Because of the use of a highly permeable membrane and better preservation of the residual renal function, it could be anticipated that some of these uremic toxins are more efficiently cleared across the peritoneal membrane, and that the plasma and tissue levels of these compounds are lower than in hemodialysis patients. This article analyzes the generation and removal of several uremic toxins in peritoneal dialysis patients. The following uremic toxins are discussed: β_2-microglobulin, advanced glycation end products, advanced oxidation protein products, granulocyte inhibitory proteins, p-Cresol, and hyperhomocysteinemia. Some recent studies are reviewed suggesting that uremic toxins are involved in the progression of renal failure and are at least partially removed by peritoneal dialysis. We conclude that, although the plasma levels of some of these compounds are lower in peritoneal dialysis versus hemodialysis patients, it does not mean that the peritoneal dialysis patient is "better" protected against the numerous disturbances caused by these toxins.

It is now well accepted that the compounds accumulating in the uremic blood and tissues during the development of end-stage renal disease have either a direct or indirect impact on several biochemical and physiologic functions, as recently reviewed by Bergström [1] and our group [2, 3].

The recognition that uremic complications are related at least in part to the accumulation of these toxic substances has led to efforts not only to identify them or to inhibit their generation but also to enhance their detoxification or their removal by dialysis procedures. Much attention has been paid to the effect of hemodialysis on the removal of these toxins, while relatively less is known on their behavior in peritoneal dialysis.

However, because of the use of highly permeable peritoneal membranes and better preservation of the residual renal function in peritoneal dialysis, it could be anticipated that some of these uremic retention solutes are cleared more efficiently in peritoneal dialysis compared to hemodialysis.

Key words: end-stage renal disease, residual renal function, hyperhomocysteinemia, p-Cresol, β_2-microglobulin, advanced glycation end products, advanced oxidation protein product.

This review will attempt to summarize the patterns of generation and removal of several uremic toxins in peritoneal dialysis patients.

For reasons of space, the discussion will be limited to β_2-microglobulin (β_2m), advanced glycosylation end products (AGEs), advanced oxidation protein products (AOPPs), granulocyte inhibitory proteins, p-Cresol, and homocysteine. The potential role of the peritoneal elimination of some of these toxins on the progression of chronic renal failure, that is, the decline in residual renal function, will be discussed as well.

β_2-MICROGLOBULIN

Several studies have demonstrated lower plasma levels of β_2m in peritoneal dialysis patients than in hemodialysis patients and this has mainly been explained by a better preservation of the residual renal function in peritoneal dialysis patients [4–7]. An inverse relationship between blood levels of β_2m and residual renal function has been observed repeatedly in peritoneal dialysis [5, 6].

However, some studies found also lower blood levels for β_2m in peritoneal dialysis patients when patients were matched for residual renal function [7].

The most important biological alteration that has been related to β_2m is dialysis-related amyloidosis (DRA), which is characterized by amyloid deposition mainly in bone, joint and tendon structures, presenting as carpal tunnel syndrome, destructive arthropathy, and subchondral bone erosions and cysts. β_2-microglobulin has been demonstrated to be a major constituent of DRA-related amyloid fibrils. Recent studies have suggested a pathogenetic role of a newly modified β_2m, that is, the advanced glycation end products (AGE) formed with carbonyl compounds derived from autoxidation of both carbohydrates and lipids ("carbonyl stress") [reviewed in 8]. The lower blood levels of β_2m in peritoneal dialysis patients may explain the lower prevalence of β_2m-related amyloidosis. For example, Nomoto et al registered carpal tunnel syndrome in only 7 patients among a total of 5050 CAPD patients (0.14%) in a multicenter study in Japan [9]. In a recent multicenter European autopsy study, the incidence of amyloid in the peritoneal dialysis patients

was also lower compared to hemodialysis patients, even when the patients were matched for duration of dialysis therapy, although the difference was not statistically significant [10].

On the other hand, Tan et al performed serum amyloid component P scintigraphy, a specific technique for the detection of amyloid deposits, and found that the prevalence of positive scans in peritoneal dialysis patients was similar to that in hemodialysis patients [11].

The effects of 3-deoxyglucosone (3-DG), a potent protein cross-linking intermediate of the Maillard reaction, on the AGE modification of β_2m were studied, and the serum levels of 3-DG in patients undergoing hemodialysis, continuous ambulatory peritoneal dialysis (CAPD) and undialyzed patients were quantitated [12]. The serum levels of 3-DG were markedly increased in the dialyzed and undialyzed uremic patients. Incubation of β_2m with 3-DG at 37°C resulted in the emission of fluorescence characteristic for AGE, and caused AGE modification and dimer formation of β_2m, as demonstrated by Western blotting. The AGE-modified dimer of β_2m could be extracted from the amyloid tissue of a patient with DRA. 3-DG showed more intense and faster reactivity with β_2m to form AGE and the dimer as compared with glucose, and aminoguanidine suppressed the AGE and dimer formation of β_2m by 3-DG. It was concluded that the 3-DG accumulating in uremic serum may be involved in the AGE modification of β_2m amyloid.

ADVANCED GLYCATION END PRODUCTS

Advanced glycation end products (AGEs) are formed during nonenzymatic glycation and oxidation (glycoxidation) reactions. AGE accumulation in uremia cannot be attributed to hyperglycemia nor simply to a decreased removal by glomerular filtration. Recent evidence has suggested that, in uremia, the increased carbonyl compounds derived from carbohydrates and lipids modify proteins not only by glycoxidation reaction, but also by a lipoxidation reaction ("carbonyl stress"). Carbonyl stress has been implicated in the content derived from the high glucose of the CAPD solution, from solutes being the end products of heat sterilization of the solution, and from uremic retention. Carbonyl stress might not only modify peritoneal matrix proteins and alter their structures, but also react with mesothelial and endothelial cell surface proteins and initiate a range of inflammatory responses. Carbonyl stress might therefore contribute to the development of peritoneal sclerosis in patients with long-term CAPD [reviewed in 13,14].

In CAPD patients, the peritoneal membrane is continuously exposed to the high glucose concentration contained in the dialysate, and this may lead to the local generation of AGEs. To test this hypothesis, the plasma and dialysate AGE concentrations in five CAPD patients were evaluated. The dialysate was measured after a one-hour and after a 12-hour dwell time. Additionally, an immunohistochemical investigation of the peritoneal membrane for AGE was performed in two patients [15]. Only low concentrations of AGE were found in the dialysate after a one-hour dwell time; however, after 12 hours the dialysate AGE was even greater than the plasma concentration. Positive staining for AGE in the interstitium of the mesothelial layer was observed in both peritoneal specimens. The dialysate AGE contained a high proportion of high-molecular-weight AGE proteins and low-molecular-weight AGE was found to be in the same concentration range as the total serum AGE. It was therefore concluded that there is local generation of AGE in the peritoneal membrane and a "washing out" of AGE from the peritoneal membrane during longer dwell times. Other studies have also shown that formation of AGE products occurs in dialysis fluid and that factors such as pH and lactate in dialysate can modulate this process [16].

Another study confirmed that AGEs become predominantly accumulated in the vascular wall in accordance with the prolongation of CAPD treatment, and this might play a role in the increased permeability of the peritoneal membrane in CAPD [17].

In CAPD patients, AGE formation in the peritoneum correlates with the development of severe interstitial fibrosis and microvascular sclerosis, which is associated clinically with impaired peritoneal ultrafiltration. In patients with low peritoneal ultrafiltration, AGE accumulated in the peritoneal fibrous tissue and microvascular walls. Remarkably, AGE accumulated more intensely in hyalinized fibrosis of small venular media. The extent of AGE accumulation in peritoneal interstitium and vascular walls correlated with the progression of interstitial fibrosis and vascular sclerosis [18].

Furosine and pentosidine are examples of early and late glycation products, respectively. Plasma furosine and pentosidine were measured by HPLC in patients with renal dysfunction with or without diabetes mellitus, and dialysate pentosidine and furosine in CAPD patients. Plasma furosine was remarkably high in diabetes mellitus, hemodialysis, and CAPD patients. Plasma pentosidine appeared to depend on renal function and was not influenced by diabetic condition. Plasma pentosidine was significantly higher in CAPD than hemodialysis patients. A weak positive correlation was noted between dialysate and plasma furosine and pentosidine, indicating the main source of furosine and pentosidine in peritoneal dialysis effluent to be plasma. Thus, in situ formation of early glycation products in the peritoneal cavity takes place in CAPD patients, and high plasma pentosidine may lead to its accumulation in tissue, resulting, possibly, in pathological changes [19].

Pannekeet et al recently demonstrated that four-hour

pentosidine effluent contents are not influenced by dialysate glucose concentration or osmolality of the dialysate, in contrast to percentage glycation of albumin and IgG [20]. The relationship between the pentosidine effluent contents and duration of peritoneal dialysis, and the effect of nonglucose dialysate on the pentosidine effluent contents suggest that long-term glucose exposure is an important determinant of membrane glycosylation. Thus, pentosidine effluent contents probably reflect the long-term effects of intraperitoneal glycosylation of peritoneal membrane proteins. Six patients with peritoneal ultrafiltration failure were treated with nonglucose dialysis solutions and the pentosidine effluent contents were studied after six weeks. In five of six patients treated with nonglucose dialysate, pentosidine effluent contents decreased while serum pentosidine was stable, suggesting that treatment with nonglucose dialysis solutions may result in a "washout" of glycosylated proteins from the peritoneal membrane [20].

The peritoneal kinetics of pentosidine were first studied by Friedlander et al [21, 22]. The glycated content of peritoneal proteins was initially identical to plasma, but increased 200% within four hours due to in situ glycation, and this also was demonstrated in vitro. In contrast, peritoneal proteins contained a two to four times greater content of the AGE pentosidine at all equilibrium time points. It was concluded that the clearance of protein-associated pentosidine by the peritoneal membrane may explain the lower steady state levels in patients treated by peritoneal dialysis.

Miyata et al demonstrated that pentosidine accumulates markedly as an albumin-linked form and in a free-form in the plasma of patients with end-stage renal failure [23]. In a follow-up study, it appeared that hemodialysis cleared free pentosidine, but not albumin-linked pentosidine [24]. In contrast, CAPD cleared both forms. Plasma total pentosidine levels were significantly lower in CAPD than in hemodialysis, in part as the result of a lower serum albumin level in the former patients. However, the free pentosidine was also significantly lower in CAPD than in hemodialysis. The transport of both the free and albumin-linked pentosidine across the peritoneum occurs mainly by diffusion. Interestingly, peritoneal albumin-linked pentosidine clearance significantly exceeded albumin clearance. The fact that albumin-linked pentosidine levels were significantly higher in the peritoneal fluid than in the serum raises the intriguing possibility of a facilitated diffusion of albumin-linked pentosidine or an active transport mechanism for protein-linked pentosidine into the peritoneal cavity.

It has previously been shown that glucose solutions that were heat-sterilized showed an increase in UV absorbance at 284 nm and were cytotoxic [25]. These and subsequent results indicated that the toxic products formed during heat sterilization of PD fluids are derived from glucose [25, 26]. Among these toxic products, the dicarbonyl compound 3-DG, is produced. The 3-DG concentrations in commercially and laboratory-prepared heat-sterilized fluids were 118 and 154 μmol/L, respectively. Gambrosol-Bio dialysate produced through an alteration of the manufacturing condition, and sterile-filtered fluid produced in the laboratory contained 3-DG in concentrations of 12.3 and less than 1.2 μmol/L, respectively. It can be speculated that the presence of 3-DG in unused conventional peritoneal dialysis–fluid could act as a local promoter, and increase local AGE formation within the peritoneal cavity [27].

In vitro studies have shown that heat-sterilized icodextrin (polyglucose) peritoneal dialysis fluid results in less glycation and AGE formation than conventional heat-sterilized glucose dialysate [28].

ADVANCED OXIDATION PROTEIN PRODUCTS

Like lipids, amino acids, peptides and proteins are vulnerable to attacks by a variety of free radicals and related oxidants, and high levels of advanced oxidation protein products have been found in the plasma of uremic patients [29–31]. Interestingly, the plasma levels of these AOPPs were lower in CAPD patients than in hemodialysis patients. Furthermore, a close correlation was found between the AOPP levels and the AGE-pentosidine levels linking the Maillard reaction to oxidative pathway of injury to biological molecules [29].

GRANULOCYTE INHIBITORY PROTEINS

A peptide that inhibits the chemotactic movement of polymorphonuclear leukocytes in a concentration dependent, nonreversible manner was recently isolated from the peritoneal effluent of CAPD patients [32, 33]. Amino acid sequencing showed that the isolated peptide has the same amino-terminal sequence as ubiquitin. The same group had previously isolated two other granulocyte inhibitory proteins (GIP I and GIP II) with homology to light chain proteins and β_2m, respectively [34]. It was speculated that these proteins were responsible, at least in part, for impaired local cellular host defense in the peritoneal cavity.

p-CRESOL

p-Cresol is a phenolic and volatile compound with a molecular weight of only 108.1 D. It is partially lipohilic and binds strongly to plasma proteins (close to 100%) under normal conditions. p-Cresol is an end product of protein breakdown produced by the intestinal bacteria, as a result of the metabolism of tyrosine and phenylalanine, and an increase of the nutritional protein load in

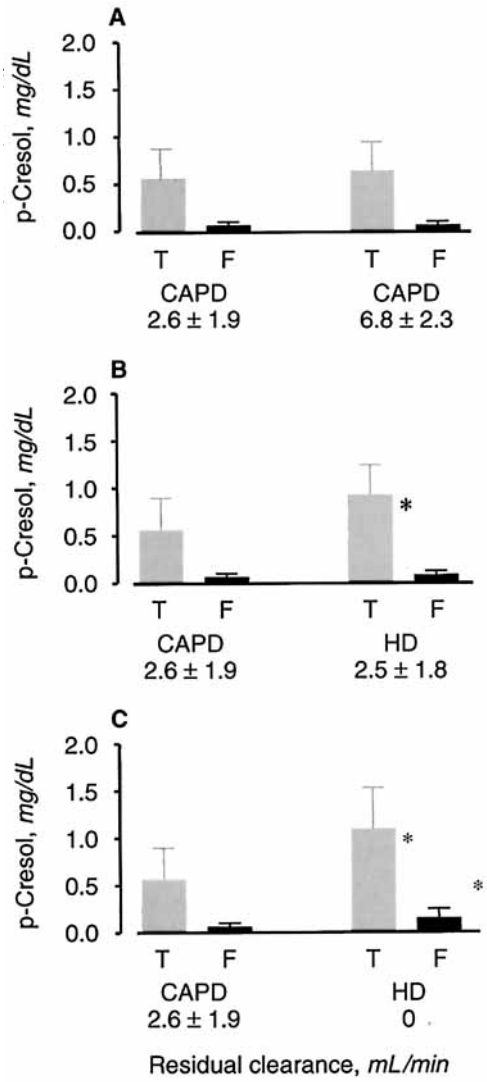

Fig. 1. Plasma levels of total (T) and free (F) p-Cresol in continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD) patients. (*A*) p-Cresol levels in two groups of CAPD patients with different residual renal function. (*B*) p-Cresol levels in CAPD and hemodialysis patients matched for residual renal function. The plasma levels of total p-Cresol are significantly higher in the hemodialysis patients. (*C*) p-Cresol plasma levels in CAPD patients and anuric patients treated with hemodialysis. Both the total and free levels of p-Cresol are significantly higher in the hemodialysis patients.

healthy individuals results in its enhanced generation and urinary excretion [35]. The serum concentration of p-Cresol is elevated in renal failure [2]. Recently, a sensitive method to determine total and free p-Cresol has been developed [36]. As illustrated in Figure 1, the total and free levels of p-Cresol seemed to be lower in CAPD compared to levels found in hemodialysis. These differences remained significant even after correction for differences in residual renal function between peritoneal dialysis and hemodialysis patients. At present, p-Cresol has been linked to several disturbances of biological functions in uremia, amongst others the phagocytic response to bacterial load [reviewed in 35].

HYPERHOMOCYSTEINEMIA

The high prevalence of cardiovascular disease in ESRD that is not explained by the classic risk factors, has been clarified considerably by the linkage of hyperhomocysteinemia, a common finding in ESRD, with an increased risk of cardiac disease and atherosclerosis [37–39].

Total homocysteine (Hcy) values averaged 29.8 μmol/L in hemodialysis patients, significantly higher than the mean value of 19.9 μmol/L observed in patients on peritoneal dialysis ($P < 0.001$). The prevalence of hyperhomocysteinemia was 90.8% among hemodialysis patients, significantly higher than the prevalence of 67.4% among peritoneal dialysis patients. Folate values in hemodialysis patients averaged 45.5 nmol/L and were significantly lower than in peritoneal dialysis patients [40]. Folate deficiency has been linked to hyperhomocysteinemia.

A common polymorphism in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene (C677T transition) results in increased total homocysteine levels in peritoneal dialysis patients compared to age- and sex-matched healthy individuals. The allelic frequency of the C677T transition in the *MTHFR* gene in peritoneal dialysis patients (0.29) was, however, comparable to the frequency in healthy individuals (0.34) [41].

The peritoneal elimination of total homocysteine primarily depends on the plasma total homocysteine concentration. Elevated total homocysteine plasma levels cannot be reduced efficiently by peritoneal dialysis [42]. In contrast, a significant and prolonged reduction in Hcy concentrations by peritoneal dialysis in ESRD patients was observed by Ducloux et al [43]. The decrease in Hcy concentration was positively related to dialysis adequacy. This study suggests the possibility that dialysis adequacy may influence arteriosclerotic outcomes through a Hcy-lowering effect.

Hyperhomocysteinemia can be normalized with folic acid alone in about 40% of peritoneal dialysis patients. Betaine does not further lower plasma homocysteine levels. A maintenance dose of 1 or 5 mg folic acid daily results in equivalent plasma homocysteine levels. Long-term reduction in plasma homocysteine did not result in an improvement of endothelial function as assessed by determination of endothelium-dependent vasodilation and biochemical markers [44].

Methionine-containing amino acid containing peritoneal fluid induces an increase in the plasma total homocysteine level. This has the potential to offset the beneficial effects of an improved serum lipid profile and reduced fat mass on the risk of cardiovascular disease in peritoneal dialysis patients. Therefore, lowering the methionine con-

tent of the fluid may be required to overcome this adverse effect [45].

ROLE OF UREMIC TOXINS IN THE PROGRESSION OF RENAL FUNCTION

An interesting study explored the possibility that circulating uremic toxins were involved in the progressive loss of intact nephrons in chronic renal failure [46]. This loss is attributed to progressive sclerosis at the level of the glomeruli of the intact nephrons. Rats underwent subtotal nephrectomy and a kidney biopsy after seven weeks and the extent of glomerular sclerosis was semiquantitatively estimated. One group of animals was treated with peritoneal dialysis, while another group received an oral charcoal adsorbent, called AST-120. The animals were then re-examined by micropuncture and histology at week 12. The group of animals that was treated with peritoneal dialysis showed lesser glomerulosclerosis than the control group at the end of the experiment and the percentage of glomeruli with a higher sclerosis index was much higher in the undialyzed animals. Also, the glomerular filtration rate was significantly higher at 12 weeks in the dialyzed animals. These results were taken as evidence that biologically active circulating substances released in uremia are involved in the progression of glomerular sclerosis and that peritoneal dialysis can at least partially remove these substances.

Other uremic toxins like albumin-bound furancarboxylic acid, an inhibitor of erythropoiesis, show lower blood levels in peritoneal dialysis compared to hemodialysis patients, and this can also be explained by a more efficient removal across the peritoneal membrane [47].

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